

Distinguished lecturer examines the biology of Alzheimer's disease

By Robin Arnette

The hippocampus is a small structure in the brain primarily involved in learning and memory, but a growing body of research suggests it is also implicated in several illnesses, such as Alzheimer's disease, cognitive aging, depression, and schizophrenia. These disorders are mechanistically distinct, so how can the same structure be associated with such a diverse range of conditions?

Scott Small, M.D., is one of several neurologists interested in that question. His work with functional imaging has shown that part of the answer is due to the hippocampus being made of several different cell types, rather than one. Small presented his findings April 14 during his NIEHS distinguished lecture titled, "Isolating Pathogenic Mechanisms Embedded Within the Hippocampal Circuit Through Regional Vulnerability." David Armstrong Ph.D., of the NIEHS Neurobiology Laboratory, served as seminar host.

Functional imaging reveals earliest signs of illness

Small

(<http://web.neuro.columbia.edu/members/profiles.php?id=86>)

is the Boris and Rose Katz Professor of Neurology and Director of the Alzheimer's Disease Research Center at Columbia University in New York. He said the imaging technology that allows his group to study the hippocampus has only been around since the beginning of this century.

The term functional imaging means that the cameras used in this research are sensitive to changes in the metabolism of neurons. Cerebral blood volume functional magnetic resonance imaging, or CBV-fMRI, is not the only tool that can measure neuronal metabolic changes, but it is the only one that offers submillimeter resolution of hippocampal cells, which allows the ability to quantify measurements. It is also applicable to a variety of species.

"CBV-fMRI allows us to generate spatial maps in patients versus controls and ask what part of the hippocampus is linked to different disorders," Small said.

According to Small, Alzheimer's disease progresses through four major stages — preclinical; prodromal, or the earliest indication of symptoms; mild cognitive; and dementia. The areas of the hippocampus that show a loss of cerebral blood volume or loss of function show up in color on images from CBV-fMRI cameras. Small's research was able to determine that cells in a part of the brain called the lateral entorhinal cortex (LEC) start to show signs of sickness during the preclinical stage, perhaps several years before cell death and symptoms of Alzheimer's begin.

Linked Video

[Watch as Small explains the complexity of Alzheimer's disease in this video from Columbia University. \(2:46\)](#)

Alzheimer's may result from dysfunction in cellular transport

The brain mapping work also found that another part of the brain called the dentate gyrus (DG) becomes dysfunctional during the normal process of aging. However, it was relatively resistant to Alzheimer's. Analysis of both the LEC and DG highlighted a molecule, called retromer, that is involved in the origin of Alzheimer's disease.

Small explained that retromer is a multimodule protein complex involved in the transport of molecules from the endosome, which is a cellular sac that sorts particles moving into and throughout the cell. He said that amyloid precursor protein, which is the progenitor of the amyloid plaques that form in the brains of Alzheimer's patients, gets chopped up after it leaves the endosome. If retromer does not remove these fragments, they become neurotoxic to the cells. Studies in which retromer was knocked out showed an increase in brain plaques, and an increase in retromer showed a decrease in brain plaques.

Because retromer is made up of several modules, Small and his team thought that increasing the modules' ability to stick to each other would be a viable approach to drug design. "We developed chaperones, or proteins that bind two of the modules very tightly, and it increased retromer stability," Small said. "The chaperone also decreased amyloid formation."

Small discussed two other pathologies associated with Alzheimer's, which included the contribution of microglia cells and



Although the majority of Small's talk focused on Alzheimer's disease, he said mapping patterns of brain dysfunction could lead to clues about other diseases. (Photo courtesy of Steve McCaw)



"Dr. Small has uncovered a fundamental insight into the relationship between aging and Alzheimer's disease, which affect different areas of the hippocampus, but together produce one of our most devastating afflictions," Armstrong said. (Photo courtesy of Steve McCaw)

a protein called tau. Because retromer also plays a role in these pathologies, Small and his colleagues are a little closer to understanding the disease.



"The seminar was a really nice combination of brain imaging with a molecular understanding of the results," said Geoffrey Mueller, Ph.D., a staff scientist in the NIEHS Nuclear Magnetic Resonance Group. (Photo courtesy of Steve McCaw)

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